

THE VITAMINS

Chemistry, Physiology, Pathology

VOLUME I

EDITED
BY

W. H. SEBRELL, JR.

*Director, National Institutes of Health
Bethesda, Maryland*

ROBERT S. HARRIS

*Department of Food Technology
Massachusetts Institute of Technology
Cambridge, Massachusetts*



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THE VITAMINS

Chemistry, Physiology, Pathology

VOLUME I

CONTRIBUTORS TO VOLUME I

- FRANK H. BETHELL (491-506, 522-523)*
The Thomas Henry Simpson Memorial
Institute for Medical Research
University of Michigan
Ann Arbor, Michigan
- KARL A. FOLKERS (397-417, 443-448)
Organic and Biochemical Research
Division
Merck & Co., Inc.
Rahway, New Jersey
- PAUL GYÖRGY (527-593, 595-618)
Department of Pediatrics
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania
- ROBERT S. HARRIS (3, 179-180, 396, 526)
Department of Food Technology
Massachusetts Institute of Technology
Cambridge, Massachusetts
- H. H. INHOFFEN (87-106)
Organisch-Chemisches Institut der
Technischen Hochschule
Braunschweig, Germany
- THOMAS H. JUKES (421-443, 448-491,
507-522)
Department of Nutrition and Physi-
ology Research
Lederle Laboratories
Pearl River, New York
- L. W. MAPSON (211-242)
Low Temperature Research Station
Department of Scientific and Indus-
trial Research
Cambridge, England
- KARL E. MASON (137-163, 171-175)
Department of Anatomy
School of Medicine and Dentistry
University of Rochester
Rochester, New York
- FRED H. MATTSON (163-170)
Chemical Division
Miami Valley Laboratories
Procter and Gamble Co.
Cincinnati, Ohio
- NICHOLAS A. MILAS (4-58)
Department of Chemistry
Massachusetts Institute of Technology
Cambridge, Massachusetts
- MAMIE OLLIVER (242-268)
Chivers and Sons, Ltd.
Cambridge, England
- H. POMMER (87-106)
Organisch-Chemisches Institut der
Technischen Hochschule
Braunschweig, Germany
- MARY ELIZABETH REID (269-347, 380-388,
391-393)
National Institutes of Health
Bethesda, Maryland
- FRED SMITH (180-211)
Division of Agricultural Biochemistry
University of Minnesota
St. Paul, Minnesota
- ESMOND E. SNELL (593-595)
Department of Chemistry
University of Texas
Austin, Texas
- RICHARD W. VILTER (348-380, 388-391)
Cincinnati General Hospital
Cincinnati, Ohio
- GEORGE WALD (59-87)
Biological Laboratories
Harvard University
Cambridge, Massachusetts
- WILLIAM L. WILLIAMS (421-443, 448-491,
507-522)
Lederle Laboratories
Pearl River, New York
- S. BURT WOLBACH (106-137)
Division of Nutritional Research
The Children's Hospital
Boston, Massachusetts
- DONALD E. WOLF (397-417, 443-448)
Merck & Co., Inc.
Rahway, New Jersey
- H. M. WUEST (417-421)
137 Summit Avenue
Montclair, New Jersey

* Numbers in parentheses indicate the pages on which each author's contribution or contributions may be found.

PREFACE

The story of vitamins resembles, in many ways, the story of the Tower of Babel. What once seemed simple has become confounded; what once could be mastered by a few is now only partly understood by the many. The very large number of publications dealing with the many aspects of vitamin research confronts the investigator and practitioner like a strange and newly discovered land, each area with its own special interests.

In this book the editors have attempted to provide, as it were, a guide service to these new and complicated areas. Just as guides are chosen for their special knowledge of each specific region, so each contributor to this work has been chosen for his competence in a specific field. For this reason no contributor has discussed one vitamin entirely, and some have discussed the same aspect of knowledge regarding several vitamins. This method will force the reader to change guides as he progresses through each chapter, but it will assure a higher level of competence than if one guide were to attempt to summarize critically and to present adequately the current knowledge concerning the chemistry, industrial production, physiology, biochemistry, estimation, occurrence, deficiency effects, pharmacology, and requirements of each vitamin. Since this is essentially a reference work, some repetition of information in the various sections of each chapter is unavoidable and even desirable.

Neither the clinical manifestations of vitamin deficiencies nor their treatments have been presented in detail, since they are adequately covered in other publications. For the same reason, the methods of vitamin assay are discussed but briefly.

Special emphasis has been given to the chemistry and physiology of the vitamins. This compelled the omission of historical material, except where it bears importantly on current knowledge. An extensive bibliography has been included so that the student can readily consult original material.

The vitamins are presented alphabetically because there is no biological reason why they should be arranged otherwise.

The editors want to express their appreciation to the authors for their scientific devotion and to the publisher for his unending patience. They will feel repaid for their labors if this work contributes to a better understanding of the role of vitamins and stimulates further research, for it has been said truly:

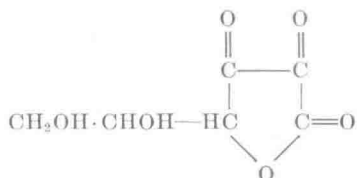
*Wisdom is the principal thing; therefore get wisdom; and with
all thy getting get understanding.*—(Proverbs IV.7)

W. H. SEBRELL, JR.
ROBERT S. HARRIS

THE VITAMINS, VOLUME I

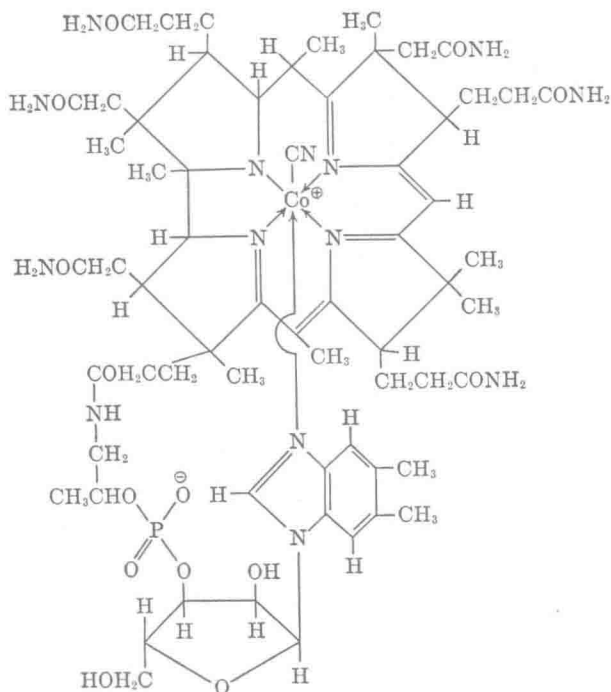
ADDENDA AND ERRATA

1. Vol. I, p. 3: Chemical name should read:
3,7 - Dimethyl - 9 - (2,6,6 - trimethyl - 1 - cyclohexen - 1 - yl)-
2,4,6,8-nonatetraen-1-ol
2. Vol. I, p. 179: Chemical name should read:
L-Threo-2,3,4,5,6-pentahydroxy-2-hexenoic acid gamma-lactone
3. Vol. I, p. 180: Formula for Dehydroascorbic acid (oxidized form)
should read:

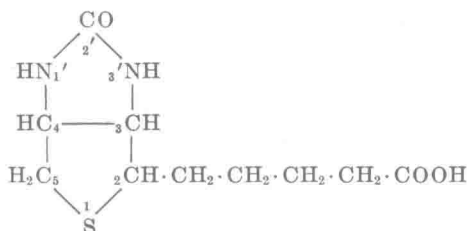


Dehydroascorbic acid
(oxidized form)

4. Vol. I, p. 396: Empirical formula: $C_{63}H_{90}O_{14}N_{14}PCo$
5. Vol. I, p. 411: Structural formula



6. Vol. I, p. 449: 4th line from bottom: Name should read 1,5-benzodiazepine
7. Vol. I, p. 541: Bottom of the page. Structural formula for Biotin should read:

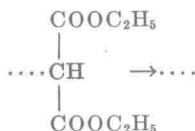


Biotin

8. Vol. I, p. 558: Lines 17 and 18 from top: Chemical name should read:
dl-cis-3,4-diamino-2-tetrahydrofuranvaleric acid
9. Vol. I, p. 568: Table, 4th line from bottom. Chemical name should read:
dl-4-Butyl-5-methyl-2-imidazolidone
10. Vol. I, p. 570: Formulas on bottom of page should read:

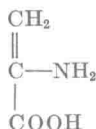


11. Vol. I, p. 573: Formula 13 should read:



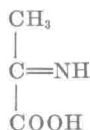
X should read = *d*-Camphorsulfonic acid

12. Vol. I, p. 582: 3rd line from bottom. Second formula from left should read:



α -Aminoacrylic acid

Third formula from left should read:



Iminopyruvic acid

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I. Nomenclature and Formulas

ROBERT S. HARRIS

Accepted names: Vitamin A
 Neovitamin A
 Axerophthol (vitamin A₁)
 Carotene

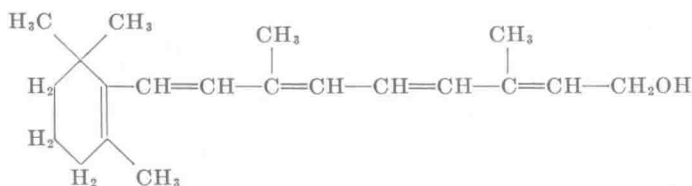
Obsolete names: Fat-soluble A
 Biosterol
 Ophthalamine
 Anti-infective vitamin

Empirical formulas: Vitamin A: C₂₀H₃₀O

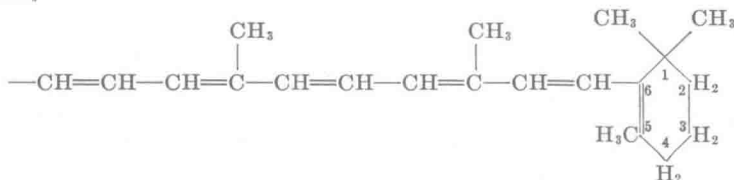
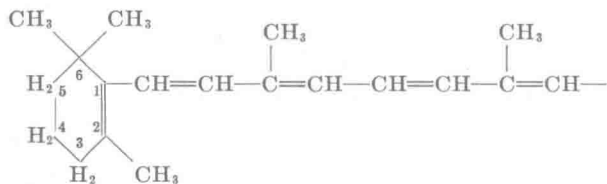
β -Carotene: C₄₀H₅₆

Chemical name: 3,7-Dimethyl-9-(2,6,6-trimethyl-2-cyclohexen-1-yl)-
 2,4,6,8-nonatetraen-1-ol

Structures:



Vitamin A



β -Carotene

II. Chemistry and Industrial Preparation

NICHOLAS A. MILAS

The chemistry of vitamin A and that of the closely related carotenoid pigments which act as precursors of this vitamin has been the subject of numerous investigations during the past three decades. Much information of lasting value has accumulated, and an attempt will be made to summarize it in the following sections.

A. THE ANTIXEROPHTHALMIC PROVITAMINS

1. INTRODUCTION

The provitamins A are carotenoid pigments¹ which are converted to vitamin A *in vivo*, usually in the intestinal tract of animals,^{2, 3} by some as yet unknown mechanism, or *in vitro* by careful oxidative degradation.⁴⁻⁷ Chemically, provitamin A carotenoids belong to a class of organic compounds known as polyenes which are built up of isoprene units, the most common of which contain eight such units or forty carbon atoms. Carotenoids are, as a rule, hydrocarbons, but some are found to contain hydroxyl, carbonyl, and oxirane or epoxide groups.

There are some well-known characteristics common to all provitamin A carotenoids: (1) all are crystalline solid pigments; (2) in all of them one finds the arrangement of isoprene units reversed in the center of the molecule so that the methyl groups occupy the 1,6 instead of the 1,5 position, and it is this arrangement which makes it possible for the cleavage to occur in the center, thereby producing vitamin A; (3) all contain a large number of carbon-carbon double bonds, most of which are conjugated and are thereby responsible for the production of color and the characteristic absorption spectra of these molecules; (4) all contain at least one trimethylcyclohexenyl or β -ionone ring, usually in conjugation with the open carbon chain double bonds; (5) although it is now well known that all naturally occurring provitamin A carotenoids have the all-*trans* configuration, they

¹ P. Karrer and E. Jucker, Carotenoids (trans. and revised by E. A. Braude). Elsevier Publishing Co., New York, 1950.

² (a) E. L. Sexton, J. W. Mehl, and H. J. Deuel, Jr., *J. Nutrition* **31**, 299 (1946); (b) F. H. Mattson, J. W. Mehl, and H. J. Deuel, Jr., *Arch. Biochem.* **15**, 65 (1947); (c) C. E. Wiese, J. W. Mehl, and H. J. Deuel, Jr., *ibid.*, **15**, 75 (1947); A. L. S. Cheng and H. J. Deuel, Jr., *J. Nutrition* **41**, 619 (1950).

³ S. Y. Thompson, J. Ganguly, and S. K. Kon, *Brit. J. Nutrition* **3**, 50 (1949).

⁴ R. F. Hunter and N. E. Williams, *J. Chem. Soc.* **1945**, 554.

⁵ G. C. L. Goss and W. D. McFarlane, *Science* **106**, 375 (1947).

⁶ N. L. Wendler, C. Rosenblum, and M. Tishler, *J. Am. Chem. Soc.* **72**, 234 (1950).

⁷ P. Meunier, J. Jouanneteau, and G. Zwingelstein, *Compt. rend.* **231**, 1170 (1950).

are capable of existing in more than one stereochemical form. Changes of this type bring about changes not only in adsorption affinity and absorption spectra but also in biological activity. Table I shows some of the well-known naturally occurring provitamin A carotenoids together with their important sources, physical properties, and relative physiological activity.

2. ISOLATION OF PROVITAMIN A CAROTENOIDS

a. General Procedure

Well-dried and well-ground materials of either plant or animal origin are extracted in large vessels, percolators, or Soxhlet apparatus by any of the well-known solvents such as low-boiling saturated hydrocarbons, benzene, ether (peroxide-free), chloroform, trichloroethylene, ethanol, or acetone. Extraction is carried out at room temperature in an atmosphere of carbon dioxide or nitrogen. The extracts are then concentrated under a reduced pressure and the concentrates saponified at 60 to 70° with a 5 to 10 % methanolic potassium or sodium hydroxide. Water is then added, and the non-saponifiable portion extracted thoroughly with low-boiling petroleum ether. The petroleum ether extract is then partitioned with an equal volume of methanol. Carotenoids which go into the methanolic layer are known as hypophasic and usually contain groups such as hydroxyl, carbonyl, or oxirane, and those which remain in the hydrocarbon layer are known as epiphasic and are usually hydrocarbons such as α -, β -, γ -, or δ -carotenes.

The epiphasic carotenoids have somewhat small differences in molecular structure and are therefore difficult to purify by the well-known classical methods. They show, however, strong selective adsorption on various solid adsorbents such as alumina, Al_2O_3 , calcium hydroxide, $\text{Ca}(\text{OH})_2$, calcium carbonate, CaCO_3 , and zinc carbonate, ZnCO_3 , and can therefore be separated in the pure state by the chromatographic adsorption method first introduced by Tswett.⁸ (See also general references on chromatography.^{1, 9})

⁸ M. Tswett, *Ber. deut. botan. Ges.* **24**, 316, 384 (1906); *Chromophylls in Plant and Animal World*. Warsaw, 1910.

⁹ General references on chromatography:

(a) L. Zechmeister and L. Cholnoky, *Chromatographic Adsorption* (trans. from the 2nd ed. by A. L. Bacharach and F. A. Robinson). John Wiley and Sons, New York, 1941.

(b) H. H. Strain, *Chromatographic Adsorption Analysis*. Interscience Publishers, New York, 1942.

(c) T. I. Williams, *Chromatographic Analysis*. Blackie and Son, London, 1947.

(d) E. Lederer, *Chromatographic Analysis*. Hermann, Paris, 1949.

(e) L. Zechmeister, *Progress in Chromatography 1938-1947*. Chapman and Hall, London, 1950.

(f) H. G. Cassidy, *Chromatographic Analysis*. Interscience Publishers, New York, 1951.